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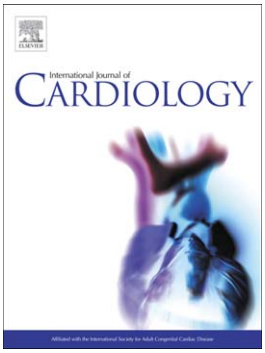

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Relation of Female Sex to Left Atrial Diameter and Cardiovascular Death in Atrial Fibrillation: The AFFIRM Trial

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ABSTRACT

Background: Female sex is associated with thromboembolism related to atrial fibrillation (AF). Left atrial (LA) diameter independently predicted incident cardiovascular (CV) major events in the general population. In AF patients, LA enlargement is associated to AF occurrence and recurrence. No data have previously been reported on the relationship between LA enlargement, sex and CV death in AF patients.

Methods and Results: All patients enrolled in the AFFIRM Trial with available data about LA dimension were included in this post-hoc analysis.

Of the 2,615 eligible for the present analysis, LA enlargement was recorded in 67.0%, more commonly in women than in men (p=0.032). Patients with LA enlargement had higher body mass index (BMI), and was more frequently hypertensive, diabetic, diagnosed with a structural heart disease, prior coronary artery disease (CAD) and heart failure (HF). BMI, left ventricular mass, female sex and mitral valve insufficiency (p<0.001) were associated with LA enlargement.

AF female patients with LA enlargement had a higher risk for CV death (p=0.011). LA diameter showed a significant association with CV death (p<0.001). Cox regression analysis demonstrated that LA diameter was an independent predictor of CV death in female AF patients (p=0.003).

Conclusions: LA diameter enlargement is associated with female sex, and carries a higher risk for CV death, particularly in females. LA diameter was an independent predictor of CV death in female AF patients.

Keywords: atrial fibrillation, women, left atrium, cardiovascular death.

1. INTRODUCTION

Atrial fibrillation (AF) is the commonest cardiac rhythm disorder which is associated with an increased risk of adverse cardiovascular (CV) outcomes, including stroke, thromboembolism, heart failure and CV death[1]. Worse clinical outcomes have been reported for female patients with AF compared to males[2].
Of note, female AF patients carry a higher risk of stroke and thromboembolism compared with males, independent of anticoagulant use[3]. Thus, female sex is included as a risk factor within the CHA_2DS_2-VASc score[4]. Independent of stroke risk, female patients with AF have higher mortality rates[5,6], even if the precise reasons accounting for this accentuated risk are poorly understood.

Left atrium (LA) enlargement has been related to higher risk of developing AF[7] and adverse CV events[8–10]. Beyond the impact on AF episode recurrences after ablation therapies[11,12], the clinical relevance of LA diameter, as assessed by trans-thoracic echocardiography, has been attributed to intracavitary thrombus formation given that LA enlargement is a surrogate marker of stroke risk[13].

On the other hand, there are conflicting results for LA enlargement in predicting all-cause death and CV events in the general population, as well as in the high risk CV population[8–10,14,15]. These discordant findings may perhaps be due to the heterogeneity of studied populations and to the lack of standardization of echocardiographic measurements. The influence of LA enlargement on CV death has been investigated in the general population showing an increased risk, particularly in males, even if this risk was mitigated by the influence of left ventricular mass (LVM)[16,17].

To the best of our knowledge, no data on LA enlargement, carefully defined according to properly echocardiographically-based sex-specific thresholds[18], and CV death have been described in AF, nor a relationship between sex and LA diameter in AF. The aim of this study was to investigate the relationship between LA diameter and sex in an AF population and second, the influence of LA enlargement on CV death

risk related to sex. To investigate these relationships, we performed a post-hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.

2. METHODS

The AFFIRM Trial was a prospective randomized trial investigating the difference of clinical outcomes between rate control versus rhythm control in the clinical management of patients with AF (ClinicalTrials.Gov Identifier: NCT00000556). United States National Heart, Lung, and Blood Institute (NHLBI) held study. This post-hoc analysis is based on the original AFFIRM database, obtained from the National Institutes of Health. The study protocol and the principal trial results have been described in detail elsewhere[19,20]. For the present analysis, all patients enrolled in the AFFIRM Trial which had available echocardiographic data about LA dimension were considered. According to the joint consensus statement between American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) for cardiac chambers quantification, LA enlargement was defined as a LA diameter greater than 3.8 cm in female patients, or >4.0 cm in male patients[18].

Thromboembolic risk was defined according to the CHA_2DS_2-VASc risk score[4]. 'Low risk' patients were defined as those males with a CHA_2DS_2-VASc score=0 or females with a CHA_2DS_2-VASc = 1; 'moderate risk' was defined as male patients with a CHA_2DS_2-VASc score = 1; 'high risk' was defined as patients with a CHA_2DS_2-VASc score ≥2[21].

2.1 Statistical Analyses

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as means and standard deviations, and tested for differences with the Student t test. Non-normal variables were expressed as median and interquartile range (IQR) and differences tested with the Mann-Whitney U test. Categorical variables, expressed as counts and percentages, were analysed by a chi-square test.

A regression analysis was performed in order to establish all clinical factors significantly associated with LA enlargement. All variables that were significantly different between the two groups at the baseline underwent a univariate analysis and those univariate predictors with a statistical significance of less than 10% were inserted into a forward multivariate logistic model. Similarly, a regression analysis was performed with the echocardiographic indexes. Next, a complete multivariable regression analysis with all variables considered in the two previous models was performed.

Kaplan-Meier (KM) curves for the occurrence of CV death, for overall population and stratified *per* male/female sex, according to LA enlargement and differences in survival distributors between subgroups was analysed using the Log-rank test. To establish clinical factors consistently associated with CV death a Cox proportional hazards analysis was performed according to sex. LA diameter, considered as a continuous variable, and all clinical variables significantly different between the two groups underwent a univariate analysis, and all variables associated to CV death with a p level <0.10 were inserted in the forward stepwise multivariate model. A two-sided p value <0.05 was considered as statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

3. RESULTS

Of the total study population of 4,060 patients originally enrolled in the AFFIRM trial, echocardiographic data about LA diameter were available for 2,615 patients (64.4%). From the overall cohort 1,048 (40.1%) patients were females and median [IQR] age was 71 [65-76] years old. Median [IQR] value for LA diameter was 4.3 cm [3.9-4.8 cm]. Of the whole cohort, 71.6% (n=1,872) were diagnosed with hypertension, whilst a previous history of coronary artery disease (CAD) was reported in 35.4% (n=927). Significant valvular disease was recorded for 331 (12.7%) patients, while a history of dilated non-ischemic cardiomyopathy was reported in 8.9% (n=234). High thromboembolic risk was recorded for 84.0% (n=2,196).

LA enlargement was recorded for the 67.0% (n=1,751), more frequently in females than in males (p=0.032) [Figure 1]. Demographic and clinical characteristics according to the presence or absence of a LA enlargement are reported in Table 1. Patients with LA enlargement were more commonly female (p=0.032) and with a higher body mass index (BMI) (p<0.001). Both hypertension and diabetes mellitus were more frequently reported in patients with LA enlargement compared to patients with normal LA diameter (p<0.001 and p=0.005, respectively). Prior myocardial infarction (MI) and CAD diagnosis were more common with LA enlargement (p=0.002), as well as heart failure (HF) p (p<0.001). Structural cardiac diseases, *e.g.* dilated non-ischemic cardiomyopathy and valvular disease, were more common in patients with LA enlargement (p<0.001). Patients with LA enlargement were at higher thromboembolic risk compared to patients with normal LA diameter (p=0.001). Patients with LA enlargement were more commonly treated with warfarin than patients with normal LA diameter (p<0.001).

Echocardiographic indexes are summarised in Table 2. Patients with LA enlargement had various functional and structural alterations in echocardiographic parameters, such as greater left ventricular mass (LVM), impaired left ventricular ejection fraction (LVEF) and mitral valve insufficiency (p<0.001). No difference was found in relative wall thickness (RWT), both defined as continuous or categorical variables.

Logistic regression analysis (Table 3) for the presence of LA enlargement showed BMI (p<0.001), female sex (p=0.022), hypertension (p=0.034), HF (p=0.001), dilated non-ischemic cardiomyopathy (p=0.040) and valvular disease (p=0.008) to be significantly associated with LA enlargement. Among echocardiographic indexes, a multivariate logistic analysis when performed with LVM, mitral valve thickening, mitral valve insufficiency and annular calcification, found that all these variables were significant associated with LA enlargement (p<0.001 and p=0.002, respectively). The final logistic model including all significant variables on univariate analysis found BMI, LVM, female sex and mitral valve insufficiency (p<0.001) to be significantly associated with LA enlargement.

Over a mean (SD) of follow-up of 3.5±1.3, there were a total of 210 CV death events. The incidence of CV death events was higher in patients with LA enlargement compared to patients with normal LA diameter, *i.e.* 2.6% patient-years *vs.* 1.6% patient-years, respectively.

Survival analysis shows that patients with LA enlargement were at higher risk of CV death (Log-Rank: 9.755, p=0.002). When performing survival analysis stratified according to sex, while difference in survival for male patients [Figure 2, Panel A] showed only a non-significant trend (Log-Rank: 3.455, p=0.063), female AF patients with LA enlargement [Figure 2, Panel B] had a significantly higher risk for CV death (Log-Rank: 6.546, p=0.011), compared to normal LA diameter.

LA diameter, as a continuous variable, showed a significant association with CV death (unadjusted hazard ratio [HR]: 1.52, 95% confidence interval [CI]: 1.22-1.89, p<0.001). A multivariable Cox regression analysis (Table 4) performed according to sex, shows that in male patients only HF and MI were independently associated to CV death (p<0.001). Conversely in female patients, BMI (p=0.001), diabetes mellitus (p<0.001), HF (p=0.001) and LA diameter (p=0.003) were independently associated with CV death.

The association between LA diameter and CV death in AF females was not mitigated when the Cox analysis was adjusted by warfarin use, aspirin concomitant therapy, LVM, left ventricular remodelling or any mitral valve abnormalities.

4. **DISCUSSION**

In the present study, LA enlargement as defined according to echocardiographically-based sex-specific thresholds, was more prevalent in AF women than men. Second, of the clinical and echocardiographic variables, female sex, BMI, LVM and mitral valve insufficiency are independently associated with LA enlargement. Finally, LA enlargement was an independent predictor of CV death in AF women, after

adjustment for confounders. Of note, the increased risk of CV death associated with LA enlargement was not influenced by LVM or mitral valve abnormalities, or by current antithrombotic therapy.

Overall, these findings emphasize the role of LA size in the prognosis assessment of AF patients, beyond AF risk of recurrence and/or stroke, and underscore the clinical relevance of LA measurement to predict CV death, particularly in female AF patients.

Many conditions are associated with LA remodelling and dilatation. LA enlargement is often the result of pressure and/or volume overload[22]. Indeed, LA enlargement due to pressure overload is usually secondary to increased LA afterload in the presence of mitral stenosis or LV dysfunction. LA volume overload can also result from mitral valve regurgitation. These LA chamber changes in cardiac hemodynamic are common in AF patients due to the high prevalence of comorbidities, such as hypertension, HF and CAD[23].

In the AFFIRM cohort, which included both valvular and non-valvular AF patients[19], a high prevalence of LA enlargement can be a reliable expression of multiple concomitant CV conditions, such as hypertension or HF. Among the various clinical variables, only BMI and female sex were independently associated with LA enlargement. Indeed, body size and sex are traditionally considered as determinants of LA size[24]. In healthy subjects, the impact of sex on LA size can partially be accounted for by differences in body size between males and females, given that females have smaller LA size that persists even after normalization for body size[25]. Interestingly, when a sex-specific assessment of LA size is performed in AF patients, LA enlargement is more prevalent in females.

Reasons for the higher prevalence of LA enlargement in AF women are uncertain. The higher frequency of clinical comorbidities such as hypertension, HF and left ventricular hypertrophy (LVH) favouring LA dilatation may only partially explain the higher LA enlargement in women. Nevertheless, we cannot exclude a sex

difference in atrial structural remodelling in AF patients perhaps related to more pronounced inflammatory *milieu* and abnormal fibrosis[26–29] in female atria, that may favour LA enlargement.

Among cardiac abnormalities commonly detected by echocardiography, mitral valve abnormalities and LVH, defined as indexed by body mass surface, are more common in AF patients. Beyond mitral valve insufficiency as a result of long-term diastolic dysfunction in AF patients, LVH is highly prevalent in non-valvular AF patients, especially in females[30]; moreover, the prognostic value of increased LVM in AF patients for all-cause death has been reported[31].

Nonetheless, data on the relationship between LA size, alone or combined with LV alterations, on both CV and all-cause death are controversial. It remains unclear whether LA size could improve prognostic evaluation independent of abnormal mitral filling pattern, increased ventricular stiffness or LVH or synergistically with these conditions. Also, LA diameter alone has been shown to independently predict all-cause[9] and CV death in the general population[17]**.** Moreover, LA enlargement predicts overall mortality in high-risk groups, for example, in dilated cardiomyopathy[32] or LV dysfunction[33], acute MI[34,35] or those undergoing valve replacement for aortic stenosis[36] and mitral regurgitation[37]. In all of these clinical scenarios, the influence of LA diameter on CV death was mitigated by LV mass[8], LVH[16] and diastolic function[38].

In the AFFIRM cohort, a trend for poor survival was observed in AF men with LA enlargement comparing to the men without. On the contrary, this difference in survival was significant in female AF patients. Thus, the incremental value of LA diameter was independently associated with CV death only in females.

As a controlled randomized clinical trial, the AFFIRM protocol allowed long-term follow-up and high quality data on several clinical variables. Also, the cohort was heterogeneous for patients' characteristics and study procedures were related to patients' baseline characteristics, while on-going clinical management was at the investigators discretion, reflecting a "real-world" setting of the clinical of AF management, thus allowing

generalizability of our results. On the contrary, limitations include the lack of data on LA volume and its impact on CV death, as well as lack of data on LA function or detailed electrophysiological mechanistic data. As our findings are based on a post-hoc analysis, they need to be confirmed in further studies specifically powered for the purpose.

In conclusion, LA diameter enlargement was associated with female sex, and carries a higher risk for CV death, particularly in females. LA diameter was an independent predictor of CV death in female AF patients.

Conflict of Interest

GYHL reports guideline membership/reviewing for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. All the other authors report no relationships that could be construed as a conflict of interest.

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Table 1: Clinical and Demographic Characteristics According to Left Atrium Diameter

	Normal LA Diameter n=864	**LA Enlargement** n=1,751	***p***
Age, ***years*** median [IQR]	70 [65-76]	71 [64-76]	1.000
SBP, *mmHg* median [IQR] *2,603*	134 [120-150]	134 [120-150]	0.843
DBP, *mmHg* median [IQR] *2,603*	78 [70-85]	78 [70-85]	0.529
BMI, ***kg/m²*** median [IQR] *1,582*	26.8 [23.9-29.9]	28.8 [25.1-32.9]	<0.001
Female Sex, n (%)	321 (37.2)	727 (41.5)	0.032
AF Episode *2,522*			0.264
First, n (%)	534 (64.2)	1,046 (61.9)	
Recurrent, n (%)	298 (35.8)	644 (38.1)	
Treatment Arm			0.813
Rate Control, n (%)	427 (49.4)	874 (49.9)	
Rhythm Control, n (%)	437 (50.6)	877 (50.1)	
Hypertension, n (%)	567 (65.6)	1,305 (74.5)	<0.001
Smoking Habit, n (%)	103 (11.9)	204 (11.7)	0.840
Diabetes, n (%)	141 (16.3)	366 (20.9)	0.005
Heart Failure, n (%)	118 (13.7)	487 (27.8)	<0.001
Coronary Artery Disease, n (%)	270 (31.2)	657 (37.5)	0.002
Myocardial Infarction, n (%)	108 (12.5)	302 (17.2)	0.002
Dilated Non-Ischemic Cardiomyopathy, n (%)	45 (5.2)	189 (10.8)	<0.001

Stroke/TIA, n (%)	111 (12.8)	227 (13.0)	0.933
Prior Cardiac Interventional Procedures	66 (7.6)	134 (7.7)	0.990
Valvular Disease, n (%)	75 (8.7)	256 (14.6)	<0.001
Peripheral Vascular Disease, n (%)	48 (5.6)	112 (6.4)	0.399
Pulmonary Disease, n (%)	104 (12.0)	227 (13.0)	0.502
Predominant Cardiac Disease			<0.001
None, (%)	154 (17.8)	164 (9.4)	
Coronary Artery Disease, n (%)	171 (19.8)	425 (24.3)	
Dilated Non-Ischemic Cardiomyopathy	25 (2.9)	112 (6.4)	
Hypertension, (%)	472 (54.6)	927 (52.9)	
Other, n (%)	42 (4.9)	123 (7.0)	
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	3 [2-4]	<0.001
CHA_2DS_2-VASc Risk Category			0.001
Low, n (%)	9 (1.0)	22 (1.3)	
Intermediate, n (%)	161 (18.6)	227 (13.0)	
High, n (%)	694 (80.3)	1,502 (85.8)	
Pharmacological Treatments			
Aspirin, n (%)	234 (27.1)	428 (24.4)	0.144
Warfarin, n (%)	688 (79.6)	1,554 (88.7)	<0.001
ARB/ACE inhibitor, n (%)	281 (32.5)	746 (42.6)	<0.001
Beta-blockers, n (%)	320 (37.0)	782 (44.7)	<0.001
Digoxin, n (%)	438 (50.7)	926 (52.9)	0.285

Diltiazem, n (%)	264 (30.6)	532 (30.4)	0.935
Verapamil, n (%)	86 (10.0)	167 (9.5)	0.738

Legend: AF= atrial fibrillation; ACE= angiotensin converting enzyme; ARB= angiotensin II receptor blockers; BMI= body mass index; DBP= diastolic blood pressure; IQR= interquartile range; LA= left atrium; SBP= systolic blood pressure; TIA= transient ischemic attack.

Table 2: Echocardiographic Indexes According to Left Atrial Diameter

	Normal LA Diameter n=864	**LA Enlargement** n=1,751	**p**
LA Diameter, *cm* median [IQR]	3.6 [3.3-3.9]	4.6 [4.3-5.0]	<0.001
LVEF, *%* median [IQR] *789*	60 [54-65]	55 [45-64]	<0.001
IVS, *cm* median [IQR] *2,159*	1.1 [1.0-1.2]	1.1 [1.0-1.3]	<0.001
LVEDD, *cm* median [IQR] *2,290*	4.8 [4.3-5.2]	5.1 [4.6-5.6]	<0.001
LVPWT, *cm* median [IQR] *2,140*	1.0 [0.9-1.2]	1.1 [1.0-1.2]	<0.001
LVM, *gr* median [IQR] *2,050*	185.98 [150.56-230.23]	213.08 [173.61-268.54]	<0.001
RWT, median [IQR] *2,087*	0.43 [0.38-0.50]	0.42 [0.37-0.49]	0.070
RWT>0.42, n (%)	394 (55.0)	711 (51.9)	0.169
Mitral Valve Thickening, n (%)	109 (12.8)	245 (14.1)	0.376
Mitral Valve Insufficiency, n (%)	99 (11.7)	433 (24.9)	<0.001
Mitral Annular Calcification, n (%)	117 (13.8)	346 (19.9)	<0.001

Legend: IQR= interquartile range; IVS= interventricular septum; LA= left atrial; LVEDD= left ventricular end diastolic dimension; LVEF= left ventricular ejection fraction; LVM= left ventricular mass; LVPWT= left ventricular posterior wall thickness.

Table 3: Logistic Regression Analysis for Left Atrial Enlargement

	Multivariate Analysis		
	OR	***95% CI***	***p***
Clinical Variables			
BMI *(Continuous Variable)*	1.07	1.04-1.09	<0.001
Sex *(Female vs. Male)*	1.30	1.04-1.63	0.022
Hypertension	1.29	1.02-1.65	0.034
Heart Failure	1.67	1.22-2.27	0.001
Dilated Non-Ischemic Cardiomyopathy	1.63	1.02-2.57	0.040
Valvular Disease	1.64	1.14-2.36	0.008
Echocardiographic Indexes			
LVM *(Continuous Variable)*	1.01	1.00-1.01	<0.001
Mitral Valve Insufficiency	2.41	1.85-3.13	<0.001
Mitral Annular Calcification	1.50	1.15-1.96	0.002
Final Model			
BMI *(Continuous Variable)*	1.05	1.02-1.07	<0.001
Sex *(Female vs. Male)*	1.73	1.32-2.28	<0.001
LVM *(Continuous Variable)*	1.01	1.00-1.01	<0.001
Mitral Valve Insufficiency	3.04	2.10-4.39	<0.001

Legend: BMI= body mass index; CI= confidence interval; LVM= left ventricular mass; OR= odds ratio.

Table 4: Multivariable Cox Regression Analysis for Cardiovascular Death According to Sex

	Multivariate Analysis		
	HR	***95% CI***	***p***
Males			
Heart Failure	2.80	1.62-4.84	<0.001
Myocardial Infarction	2.68	1.54-4.65	<0.001
Females			
BMI *(Continuous Variable)*	0.90	0.84-0.96	0.001
Diabetes	6.12	3.09-12.14	<0.001
Heart Failure	2.99	1.59-5.63	0.001
Left Atrial Diameter *(Continuous Variable)*	2.28	1.33-3.90	0.003

Legend: BMI= body mass index; CI= confidence interval; HR= hazard ratio.

Figure Legends

Figure 1: Left atrial enlargement according to sex

Legend: LA= left atrium.

Figure 2: Kaplan-Meier Curves for Cardiovascular Death According to Sex

Legend: Solid Line= Left Atrium Enlargement, Dashed Line= Normal Left Atrium Diameter.

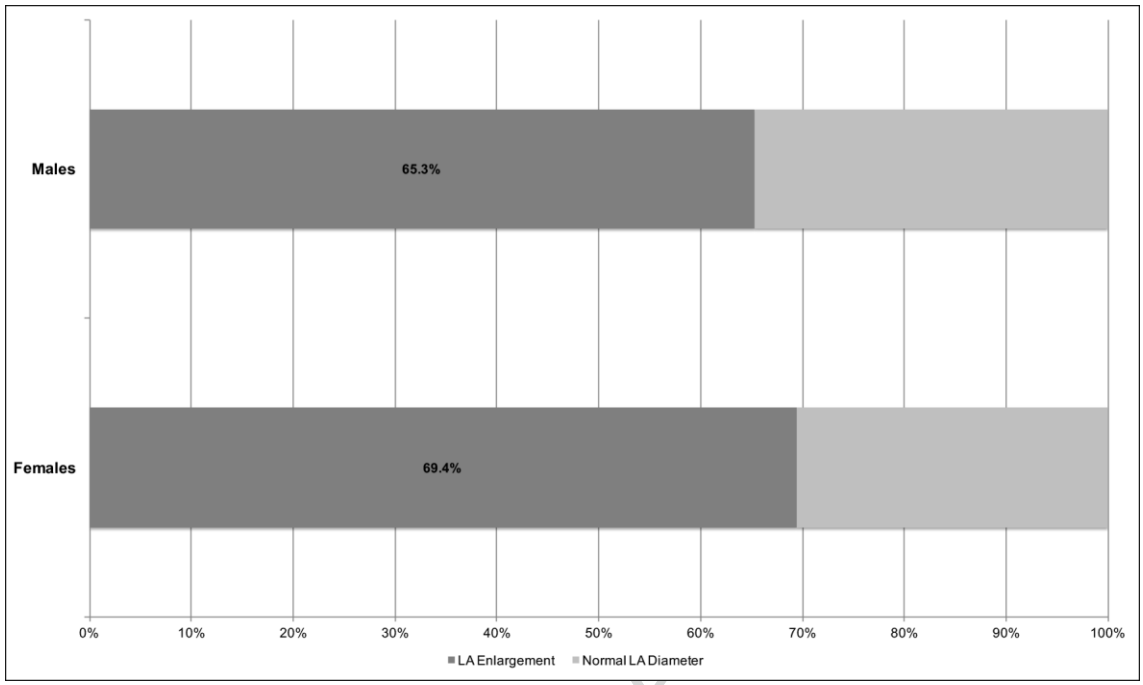

Figure 1

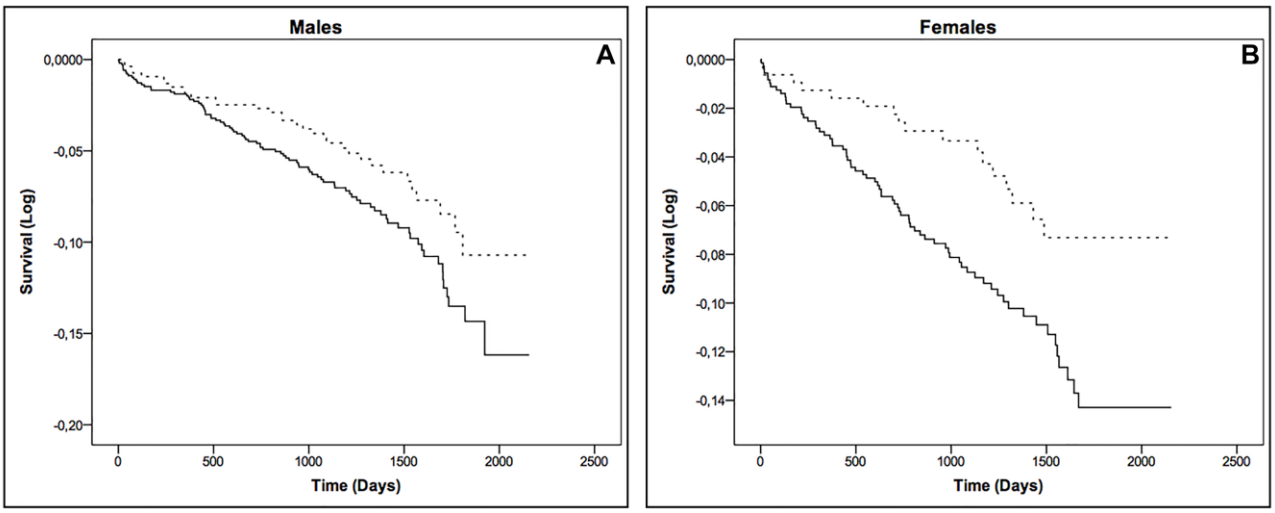

Figure 2